# ENT COOPERATION TRE

From the INTERNATIONAL BUREAU

## PCT

### NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

OTTEVANGERS, S., U.
Vereenigde
Nieuwe Parklaan 97
NL-2587 BN The Hague
PAYS-BAS

**Date of mailing** (day/month/year)
08 May 2000 (08.05.00)

**Applicant's or agent's file reference**
P22294PC00

**IMPORTANT NOTIFICATION**

**International application No.**
PCT/NL99/00352

**International filing date** (day/month/year)
04 June 1999 (04.06.99)

**1.** The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address

OTTEVANGERS, S., U.
Vereenigde Octrooibureaux
Nieuwe Parklaan 97
NL-2587 BN The Hague
Netherlands

State of Nationality:
State of Residence:
Telephone No.: 070-41 66 711
Facsimile No.: 070-41 66 799
Teleprinter No.:

**2.** The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

OTTEVANGERS, S., U.
Vereenigde
Nieuwe Parklaan 97
NL-2587 BN The Hague
Netherlands

State of Nationality:
State of Residence:
Telephone No.: 070-41 66 711
Facsimile No.: 070-41 66 799
Teleprinter No.:

**3.** Further observations, if necessary:
**The name of the agent's company has changed.**

**4.** A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☒ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

**The International Bureau of WIPO**
**34, chemin des Colombettes**
**1211 Geneva 20, Switzerland**
Facsimile No.: (41-22) 740.14.35

Authorized officer
Aino Metcalfe
Telephone No.: (41-22) 338.83.38

'ENT COOPERATION TRE,

From the INTERNATIONAL BUREAU

# PCT

## NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

OTTEVANGERS, S., U.
Vereenigde Octrooibureaux
Nieuwe Parklaan 97
NL-2587 BN The Hague
PAYS-BAS

**Date of mailing** (day/month/year)
04 November 1999 (04.11.99)

**Applicant's or agent's file reference**
P22294PC00

**IMPORTANT NOTIFICATION**

**International application No.**
PCT/NL99/00352

**International filing date** (day/month/year)
04 June 1999 (04.06.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
RIJKSUNIVERSITEIT TE GRONINGEN
Broerstraat 5
NL-9712 CP Groningen
Netherlands

State of Nationality: NL
State of Residence: NL
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
POLYGAMICS B.V.
L.J. Zielstraweg 1
NL-9713 GX Groningen
Netherlands

State of Nationality: NL
State of Residence: NL
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Aino Metcalfe
Telephone No.: (41-22) 338.83.38

# .TENT COOPERATION TRE ′

From the INTERNATIONAL BUREAU

## PCT

### NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

| | |
|---|---|
| **Date of mailing** (day/month/year)<br>28 February 2000 (28.02.00) | |
| **International application No.**<br>PCT/NL99/00352 | **Applicant's or agent's file reference**<br>P22294PC00 |
| **International filing date** (day/month/year)<br>04 June 1999 (04.06.99) | **Priority date** (day/month/year)<br>05 June 1998 (05.06.98) |
| **Applicant**<br>SPAANS, Coenraad, Jan et al | |

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

29 December 1999 (29.12.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
|---|---|
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland | Authorized officer<br>C. Villet |
| Facsimile No.: (41-22) 740.14.35 | Telephone No.: (41-22) 338.83.38 |

PATENT COOPERATION TREATY

# PCT

REC'D 28 SEP 2000

WIPO PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| P22294PC00 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/NL99/00352 | 04/06/1999 | 05/06/1998 |
| International Patent Classification (IPC) or national classification and IPC<br>C08G18/42 | | |
| Applicant<br>POLYGANICS B.V. et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 29/12/1999 | 26.09.2000 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Kolitz, R<br>Telephone No. +49 89 2399 8481 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL99/00352

## I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

| | | | | |
|---|---|---|---|---|
| 1-11 | as originally filed | | | |

**Claims, No.:**

| | | | | |
|---|---|---|---|---|
| 1-15 | as originally filed | | | |
| 16 | as received on | 03/08/2000 | with letter of | 03/08/2000 |

**Drawings, sheets:**

| | |
|---|---|
| 1/1 | as originally filed |

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**see separate sheet**

4. Additional observations, if necessary:

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 3,9-11,14 |
| | No: | Claims | 1,2,4-8,12,13,15 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 3, 9-11, 14 |
| Industrial applicability (IA) | Yes: | Claims | |
| | No: | Claims | 1-15 yes |

2. Citations and explanations

**see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**Re item I, 3.**:
The subject-matter of claim 16 filed with your letter of 03.08.00 is regarded to go beyond the disclosure as filed in the sense of Rule 70.2(c) PCT and therefore claim 16 is considered as if it had not been filed.
Claim 1 and the application as a whole concerns with a polyurethane based on polyester polymer and diol, only. Polyether components as indicated two times in claim 16 are mentioned only in the discussion of the prior art , see page 4, lines 11-18.
Therefore the subject-matter of claim 16 is regarded to go beyond the disclosure as filed in the sense of Art.34(2)b) PCT.
Consequently the examination is carried out on the basis of claims 1-15.

**Re item V:**
**Reasoned statement with regard to novelty and inventive step and industrial applicability, Article 33 (1) to (4) PCT:**
D1: EP-A-0 295 055
D2: US-A-4 284 506
D3: POLYMER BULLETIN, vol. 38, no. 2, February 1997 (1997-02), pages 211-218, XP000678622
The present claim 1 relates to a polyurethane based on diisocyanate linked "polyester polymer and diol components" the diol component having uniform block-length.
The expression "uniform block-length" is not clear, see item VIII,1.
It is also not clear as to whether or not the polyester polymer is to be counted with the diol, see item VIII, 2.

I. Lack of novelty of the subject-matter of claims 1, 2, 4-8, 12, 13 and 15 in the sense of Art. 33 (2) PCT:

1. D1 page 4, line 41 to 48 and page 5 last line to page 6 line 64, discloses an ABA triblock copolymer named PELA made by copolymerisation of polyethylene glycol chains PEG (B) with Lactic acid LA (A). The block length of the B block is determined by the molecular weight of the PEG, for instance 3400. The block length of A is determined by the degree of polymerisation of the LA sequences, for instance 209. Cf. D1, page 4, line 43 the whole polymer is then named PELA 3400 / 209. This triblock copolymer with uniform block length of the A and the B blocks as initially composed can be chain extended with diisocyanates, see D1, page 5, last line up to page 6 line 64. The resulting polyetherester urethanes

inevitably have the initially produced uniform polyol block length ABA.
Your counter argument that (B) will have a molecular weight distribution since all polymers or oligomers normally have a distribution of molecular weights set out in your letter of 03.08.00 is correct but is also applicable on the diol component of the present application having an uniform block length.
Consequently an unclear expression such as "uniform block length" cannot establish novelty in this case.
Therefore the subject-matter of claim 1 is not novel in the sense of Article 33 (2) PCT.

2. D2 example 1 discloses the reaction of a NCO-terminated polyol prepolymer B with a lactone derived polyester polyol (made of caprolacton and the polyols mentioned in Table 1) at a NCO /OH equivalent ratio of 1.1/1.0.
The NCO-terminated polyol prepolymer B in D2 column 12 is made of polyoxypropylene glycol (i.e. diol **C** in the wording of present claim 2) and MDI (which represents diisocyanate **B** in the wording of present claim 2). According to D2, example 1, the polyol prepolymer B is NCO-terminated such that it has the structure MDI-polyoxypropylene glycol-MDI or diisocyanate-diol-diisocyanate i.e. a structure **BCB** in the wording of present claim 2.
Your counter argument that prepolymer B in D2 will have a molecular weight distribution is not convincing as long as the expression "uniform block-length" is not exactly defined in present claim 1. Thus the novelty of present claim 2 cannot be established by an unclear expression such as "uniform block-length".
To achieve the NCO content of the prepolymer B of 20,5% as disclosed in D2, column 12, line 33-39 an excess of at least 2 moles of diisocyanate is necessary as disclosed in present claim 12.
According to D2 the NCO-terminated **BCB**-prepolymer prepared in D2, column 12 is reacted with a lactone derived polyester polyol (representing **A** in present claim 2 )in an equimolar ratio, such that a polyurethane of structure $(\mathbf{ABCB})_n$ is the result, similar to the formula $(\mathbf{ABCB})_n$ in present claim 2. Consequently the process is the same as disclosed in claim 13.
Moreover, the block length is the same for all diol C units as disclosed in present claim 5.
The reference to claims 1 and 2 in present claim 4 appears to be wrong since the expression "wherein E is diol" refers to claim 3, only. As long as the claim refers to claims 1 and 2 the above cited expression means only that a diol is present.

As long as the reference to claims 1 and 2 is not deleted claim 4 as a whole is not novel since a diol is present also in D2.

As set out above the polyester in D2 is a caprolactone derived polyester polyol prepared by ring opening polymerisation with the polyols mentioned in Table 1 of D2. Therefore it is also a random polyester as disclosed in present claim 6. Moreover, the random polyester in D2 is a copolyester of ε- caprolactone as disclosed in present claim 7.
Furthermore, the polyols the polyester in Table 1 of D2 is based on, are butane diol and hexane diol as set out in present claim 8.
Therefore the subject-matter of claims 1, 2, 4-8, 12 and 13 is not novel vis-à-vis D2.

3. The subject-matter of claim 15 is not novel vis-à-vis D3, see the summary, since it comprises a polyester polymer which is a diol component synthesized by chain extending polycaprolactone end-capped by diisocyanates with butane diamine. In this case the block length of the polycaprolactone units is uniform. Moreover, the polyurethane of D3 is used as implant for miniscus reconstruction, see D3 page 211, 2nd paragraph.

II. Lack of inventive step in the sense of Art.33 (3) PCT:

1. Claim 3 defines a polyurethane made of butane diisocyanate (BDI), polyesterdiol(O-D-O) and O-E-O which is butanediol, hexanediol or diethyleneglycol, having the formula BDI-O-D-O-BDI-O-E-On.
D3 comes closest to this type of polyurethane since it discloses a non toxic polyurethane urea for meniscus reconstruction made of butane diisocyanate (BDI), polyesterdiol(O-D-O) and N-E-N which is butanediamine instead of butanediol as used in present claim 3.
A replacement of butanediamine by butanediol as a chain extender in order to solve the same problem (meniscus reconstruction) is a replacement of a compound by a similar one.
The subject-matter of claim 3 appears therefore obvious in the light of D3.

2. The reaction of a lactone derived polyester polyol with the NCO-terminated BCB - prepolymer cf. D1, column 12 does not comprise a step wherein the excess NCO groups are destroyed with water. This measure appears a routine measure of the

skilled person, however. Consequently the subject-matter of claim 9 appears to be obvious.

3. A reaction product XYX of a diol and a diisocyanate is per se obvious without reference to any inventive use since the production of a XYX triblock from X and Y as disclosed in present claim 11 appears to be one of two obvious possibilities.
4. In the light of page 1, lines 21-24 of the description there may exist a prior art concerning with polyurethanes comprising copolyesters of lactide and ε-caprolactam as defined in present claim 10, such that the subject-matter of claim 10 could possibly be obvious.
   The applicant did not comment as to whether such prior art exists and filed this prior art, see Rule 5 PCT, paragraph 5.1 ii).
5. Implants based on the polyurethanes according to claim 1-10 appear to be obvious as well. The applicant has not commented as to whether the specific porosity range disclosed in claim 14 solves any technical problem. The subject-matter of claim 14 appears therefore to be obvious.

III. The subject-matter of the claims is industrially applicable.

**Re Item VIII:**

1. The expression "uniform block-length" is unclear since the degree of uniformity is not further defined in claim 1, see also page 7, line 9 of the description.
2. It is not clear as to whether or not the polyester polymer in claim 1 is to be counted with the diol. The "polyester polymer" is normally a diol and therefore it is unclear as to whether the "uniform block-length" relates only to a diol different from the polyester polyol or applies also to the polyester polymer.
3. The reference in present claim 4 to claims 1 and 2 appears to be wrong, see above point I,2.
4. In Table I on page 10 the examples which do not fall under the present claims have not been indicated as comparative. In the light of page 10, lines 20 up to page 11, line 9 of the description chain extension with uniform blocks leads only to high modulus polymers, if the uniform block is incorporated as diisocyanate (not as diol component as indicated in claim 1) in order to avoid any transesterification.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

OTTEVANGERS, Drs S.U.
VEREENIGDE OCTROOIBUREAUX
Nieuwe Parklaan 97
NL-2587 BN The Hague
PAYS-BAS

# PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 26.09.2000 |
| Applicant's or agent's file reference: P22294PC00 | **IMPORTANT NOTIFICATION** |

| International application No | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/NL99/00352 | 04/06/1999 | 05/06/1998 |

Applicant: POLYGANICS B.V. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx. 523656 epmu d
Fax. +49 89 2399 - 4465

Authorized officer

Aberribay I

Tel. +49 89 2399-8154

PATENT COOPERATION TY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| P22294PC00 | | |

| International application No | International filing date (day/month/year) | Priority date (day/month/year) |
|---|---|---|
| PCT/NL99/00352 | 04/06/1999 | 05/06/1998 |

International Patent Classification (IPC) or national classification and IPC
C08G18/42

Applicant
POLYGANICS B.V. et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 29/12/1999 | 26.09.2000 |

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx. 523656 epmu d
Fax +49 89 2399 - 4465

Authorized officer
Kolitz R.

Telephone No. +49 89 2399 8481

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No PCT/NL99/00352

## I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

| | | | | | |
|---|---|---|---|---|---|
| 1-11 | as originally filed | | | | |

**Claims, No.:**

| | | | | | |
|---|---|---|---|---|---|
| 1-15 | as originally filed | | | | |
| 16 | as received on | 03/08/2000 | with letter of | 03/08/2000 | |

**Drawings, sheets:**

| | | | | | |
|---|---|---|---|---|---|
| 1/1 | as originally filed | | | | |

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**see separate sheet**

4. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 3,9-11,14 |
| | No: | Claims | 1,2,4-8,12,13,15 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 3, 9-11, 14 |
| Industrial applicability (IA) | Yes: | Claims | |
| | No: | Claims | 1-15 yes |

2. Citations and explanations

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**Re item I, 3.:**

The subject-matter of claim 16 filed with your letter of 03.08.00 is regarded to go beyond the disclosure as filed in the sense of Rule 70.2(c) PCT and therefore claim 16 is considered as if it had not been filed.

Claim 1 and the application as a whole concerns with a polyurethane based on polyester polymer and diol, only. Polyether components as indicated two times in claim 16 are mentioned only in the discussion of the prior art , see page 4, lines 11-18.

Therefore the subject-matter of claim 16 is regarded to go beyond the disclosure as filed in the sense of Art.34(2)b) PCT.

Consequently the examination is carried out on the basis of claims 1-15.

**Re item V:**

**Reasoned statement with regard to novelty and inventive step and industrial applicability, Article 33 (1) to (4) PCT:**

D1: EP-A-0 295 055

D2: US-A-4 284 506

D3: POLYMER BULLETIN, vol. 38, no. 2, February 1997 (1997-02), pages 211-218, XP000678622

The present claim 1 relates to a polyurethane based on diisocyanate linked "polyester polymer and diol components" the diol component having uniform block-length.

The expression "uniform block-length" is not clear, see item VIII,1.

It is also not clear as to whether or not the polyester polymer is to be counted with the diol, see item VIII, 2.

I. Lack of novelty of the subject-matter of claims 1, 2, 4-8, 12, 13 and 15 in the sense of Art. 33 (2) PCT:

1. D1 page 4, line 41 to 48 and page 5 last line to page 6 line 64, discloses an ABA triblock copolymer named PELA made by copolymerisation of polyethylene glycol chains PEG (B) with Lactic acid LA (A). The block length of the B block is determined by the molecular weight of the PEG, for instance 3400. The block length of A is determined by the degree of polymerisation of the LA sequences, for instance 209. Cf. D1, page 4, line 43 the whole polymer is then named PELA 3400 / 209. This triblock copolymer with uniform block length of the A and the B blocks as initially composed can be chain extended with diisocyanates, see D1, page 5, last line up to page 6 line 64. The resulting polyetherester urethanes

inevitably have the initially produced uniform polyol block length ABA.
Your counter argument that (B) will have a molecular weight distribution since all polymers or oligomers normally have a distribution of molecular weights set out in your letter of 03.08.00 is correct but is also applicable on the diol component of the present application having an uniform block length
Consequently an unclear expression such as "uniform block length" cannot establish novelty in this case.
Therefore the subject-matter of claim 1 is not novel in the sense of Article 33 (2) PCT.

2. D2 example 1 discloses the reaction of a NCO-terminated polyol prepolymer B with a lactone derived polyester polyol (made of caprolacton and the polyols mentioned in Table 1) at a NCO /OH equivalent ratio of 1.1/1.0.
The NCO-terminated polyol prepolymer B in D2 column 12 is made of polyoxypropylene glycol (i.e. diol **C** in the wording of present claim 2) and MDI (which represents diisocyanate **B** in the wording of present claim 2). According to D2, example 1, the polyol prepolymer B is NCO-terminated such that it has the structure MDI-polyoxypropylene glycol-MDI or diisocyanate-diol-diisocyanate i.e. a structure **BCB** in the wording of present claim 2.
Your counter argument that prepolymer B in D2 will have a molecular weight distribution is not convincing as long as the expression "uniform block-length" is not exactly defined in present claim 1. Thus the novelty of present claim 2 cannot be established by an unclear expression such as "uniform block-length".
To achieve the NCO content of the prepolymer B of 20,5% as disclosed in D2, column 12, line 33-39 an excess of at least 2 moles of diisocyanate is necessary as disclosed in present claim 12.
According to D2 the NCO-terminated **BCB**-prepolymer prepared in D2, column 12 is reacted with a lactone derived polyester polyol (representing **A** in present claim 2 )in an equimolar ratio, such that a polyurethane of structure $(\mathbf{ABCB})_n$ is the result, similar to the formula $(\mathbf{ABCB})_n$ in present claim 2. Consequently the process is the same as disclosed in claim 13.
Moreover, the block length is the same for all diol C units as disclosed in present claim 5.
The reference to claims 1 and 2 in present claim 4 appears to be wrong since the expression "wherein E is diol" refers to claim 3, only. As long as the claim refers to claims 1 and 2 the above cited expression means only that a diol is present.

As long as the reference to claims 1 and 2 is not deleted claim 4 as a whole is not novel since a diol is present also in D2.

As set out above the polyester in D2 is a caprolactone derived polyester polyol prepared by ring opening polymerisation with the polyols mentioned in Table 1 of D2. Therefore it is also a random polyester as disclosed in present claim 6. Moreover, the random polyester in D2 is a copolyester of ε- caprolactone as disclosed in present claim 7.
Furthermore, the polyols the polyester in Table 1 of D2 is based on, are butane diol and hexane diol as set out in present claim 8.
Therefore the subject-matter of claims 1, 2, 4-8, 12 and 13 is not novel vis-à-vis D2.

3. The subject-matter of claim 15 is not novel vis-à-vis D3, see the summary, since it comprises a polyester polymer which is a diol component synthesized by chain extending polycaprolactone end-capped by diisocyanates with butane diamine. In this case the block length of the polycaprolactone units is uniform. Moreover, the polyurethane of D3 is used as implant for miniscus reconstruction, see D3 page 211, 2nd paragraph.

II. Lack of inventive step in the sense of Art.33 (3) PCT:

1. Claim 3 defines a polyurethane made of butane diisocyanate (BDI), polyesterdiol(O-D-O) and O-E-O which is butanediol, hexanediol or diethyleneglycol, having the formula BDI-O-D-O-BDI-O-E-On.
D3 comes closest to this type of polyurethane since it discloses a non toxic polyurethane urea for meniscus reconstruction made of butane diisocyanate (BDI), polyesterdiol(O-D-O) and N-E-N which is butanediamine instead of butanediol as used in present claim 3.
A replacement of butanediamine by butanediol as a chain extender in order to solve the same problem (meniscus reconstruction) is a replacement of a compound by a similar one.
The subject-matter of claim 3 appears therefore obvious in the light of D3.

2. The reaction of a lactone derived polyester polyol with the NCO-terminated BCB - prepolymer cf. D1, column 12 does not comprise a step wherein the excess NCO groups are destroyed with water. This measure appears a routine measure of the

skilled person, however. Consequently the subject-matter of claim 9 appears to be obvious.

3. A reaction product XYX of a diol and a diisocyanate is per se obvious without reference to any inventive use since the production of a XYX triblock from X and Y as disclosed in present claim 11 appears to be one of two obvious possibilities.
4. In the light of page 1, lines 21-24 of the description there may exist a prior art concerning with polyurethanes comprising copolyesters of lactide and ε-caprolactam as defined in present claim 10, such that the subject-matter of claim 10 could possibly be obvious.
   The applicant did not comment as to whether such prior art exists and filed this prior art, see Rule 5 PCT, paragraph 5.1 ii).
5. Implants based on the polyurethanes according to claim 1-10 appear to be obvious as well. The applicant has not commented as to whether the specific porosity range disclosed in claim 14 solves any technical problem. The subject-matter of claim 14 appears therefore to be obvious.

III. The subject-matter of the claims is industrially applicable.

**Re Item VIII:**

1. The expression "uniform block-length" is unclear since the degree of uniformity is not further defined in claim 1, see also page 7, line 9 of the description.
2. It is not clear as to whether or not the polyester polymer in claim 1 is to be counted with the diol. The "polyester polymer" is normally a diol and therefore it is unclear as to whether the "uniform block-length" relates only to a diol different from the polyester polyol or applies also to the polyester polymer.
3. The reference in present claim 4 to claims 1 and 2 appears to be wrong, see above point I,2.
4. In Table I on page 10 the examples which do not fall under the present claims have not been indicated as comparative. In the light of page 10, lines 20 up to page 11, line 9 of the description chain extension with uniform blocks leads only to high modulus polymers, if the uniform block is incorporated as diisocyanate (not as diol component as indicated in claim 1) in order to avoid any transesterification.

Claim 16

16. Biomedical polyurethane having a phase separated morphology, comprising soft segments of polyester and/or polyether components and hard segments, said hard segments consisting of a diol component having a uniform block length, and wherein the diol component on the one hand and the polyester and/or polyether components on the other hand, have been linked by diisocyanate, preferably an aliphatic diisocyanate.

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: BIOMEDICAL POLYURETHANE, ITS PREPARATION AND USE

(57) Abstract

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Inte onal Application No
PCT/NL 99/00352

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C08G18/42 C08G18/80 A61L27/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C08G A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 4 284 506 A (CASE BARTON C ET AL)<br>18 August 1981 (1981-08-18)<br>column 3, line 44 - column 8, line 21<br>examples 11,12,34-36; table 1<br>claims 1,4<br>--- | 1,2,5,6,<br>8,12 |
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
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...information on patent family members

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(54) Title: BIOMEDICAL POLYURETHANE, ITS PREPARATION AND USE

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Title: Biomedical polyurethane, its preparation and use.

The invention is directed to biomedical polyurethanes and the use thereof in various applications.

Biomedical polyurethanes (PUs) have been used for a wide range of applications. Examples include nerve guides, meniscal reconstruction materials, artificial skin and artificial veins.

For these applications, usually commercially available polyurethanes are used. These materials frequently exhibit good mechanical properties but an important disadvantage is that they contain aromatic diphenylmethane diisocyanate (MDI). MDI based polyurethanes are known to release carcinogenic and mutagenic products on degradation. Furthermore, they often show low resistance to tearing. A high resistance to tearing is important to prevent sutures from tearing out of a biomaterial. The development of new medical grade polyurethanes with good mechanical properties is therefore highly desirable.

Further an important aspect of the biomedical polyurethanes is the requirement that they can be processed into porous shaped bodies, e.g. as implants.

In the development of the novel materials of the invention, first porous 50/50 copoly(ε-caprolactone/L-lactide) materials were used for the reconstruction of meniscal lesions. They showed a very good adhesion to the meniscal tissue and, therefore, a good healing of the meniscal lesion. The mechanical properties of this copolymer resemble the mechanical properties of polyurethanes because of the high molecular weight and the presence of crystallisable L-lactide sequences. The polymer had, however, certain drawbacks. First, the degradation rate was somewhat too high. New meniscal tissue, the so called fibrocartilage, is formed after an induction time of 10 to 20 weeks.

Second, due to the very high molecular weight of the polymer a maximum concentration of 5% could be reached. This resulted in very low compression moduli of porous materials. For the ingrowth of fibrocartilage higher moduli were needed. Finally, the L-lactide crystals, which are still present after 8 years of in-vitro degradation, may induce an inflammatory reaction since cells cannot digest them unlike poly(ε-caprolactone) and polyglycolide crystals.

To avoid lactide crystallinity, an amorphous 50/50 copoly(ε-caprolactone/85,15 L,D-lactide) was used for the production of nerve guides. Due to the absence of crystals, however, this polymer showed swelling upon degradation. Therefore, the focus was put on the synthesis of ε-caprolactone and L-lactide based polyurethanes. The urethane hard segments crystals are likely to be small and susceptible to enzymatic degradation. In addition, by making an ε-caprolactone and L-lactide based PU the biocompatibility may be improved.

When the copolymer was simply chain extended with diisocyanates, the mechanical properties of the resulting polymer were poor due to the absence of a phase separated morphology. Phase separated morphologies can be reached when an isocyanate terminated polyol is chain extended with a diamine or diol resulting in a polyurethane urea and polyurethane respectively. However, the L-lactide and ε-caprolactone based prepolymer showed a deviant behavior with respect to chain extension using a diamine and diol. It appeared that the prepolymer was susceptible to aminolysis and transesterification unlike ε-caprolactone and glycolide/trimethylene carbonate prepolymers.

The invention is directed to novel biomedical polyurethanes, suitable for implants, not having the disadvantages discussed above.

Further it is an aspect of the invention to provide a novel intermediate for this polyurethane, as well as a novel way of producing the polyurethane.

In a first aspect the invention is directed to novel biomedical polyurethanes, based on diisocyanate linked polyester (co)polymer and diol components, said diol component having a uniform block-length.

According to a preferred embodiment, the polyurethane may be represented by the following formula:

$$+A-B-C-B+_n$$

wherein the B denote diisocyanate moieties, A denotes a polyester moiety, C denotes a diol moiety and n is the number of recurring units.

In a most preferred embodiment the polyurethane consists of repeating units of the following formula

$$\{C(O)-N-R_1-N-C(O)-O-D-O-C(O)-N-\ R_1-N-C(O)-O-E-O\}_n,$$

wherein $R_1$ is an n-butylene moiety, D is a polyester moiety, E is an n-butylene diol, an n-hexylene diol or a diethylene glycol based moiety and n indicates the number of repeating units.

With respect to the above formulae it is to be noted that they represent the recurring units of the polyurethane. The endgroups are not represented thereby. The nature of the endgroups will vary according to the type of (co)polyester and diol, as well as with the production process.

Further preferred embodiments of the invention are indicated in the dependent claims.

The products of the present invention show a good balance between the properties necessary for use thereof in biomedical applications, such as good modulus, tensile strength and compression modulus. It has been found possible to process these materials into porous implants by salt-leaching and freeze-drying, resulting in a material having macropores in the range of 150 µm to 300 µm. The material can

also be produced in situ in an extruder, even in combination with generating macropores in situ.

As has been indicated above, the conventional methods of producing polyurethanes may result in transesterification and aminolysis, with the consequence that the material has insufficiently balanced properties. More in particular the uniformity of block-length gets lost, resulting in loss of phase separation. The consequence thereof is that the mechanical properties deteriorate to a level below that which is acceptable for numerous biomedical applications.

An important feature of these polyurethanes is that they owe their good mechanical properties to the phase separated morphology. Because the soft segments (e.g. polyesters, polycarbonates or polyethers) are chemically incompatible with the hard segments (urethane, urea or amide moieties) phase separation occurs. The hard segments crystallize and form strong hydrogen bonds with other hard segments resulting into physical cross-links.

The behavior of these polyurethanes is in strong contrast with other polyurethanes often applied. A well-known example is polyurethanes in which 2 different, chemically incompatible, soft segments (e.g. polyesters and polyethers) are coupled by a diisocyanate. An example thereof is disclosed in US-A 4,2844,506. In this case, also a certain extent of phase separation will occur, but these materials do not owe their mechanical properties to the ability of the urethane functionality to form hydrogen bonds but to the contribution of entanglements and phase separation between the different soft segments. The reason why the urethane functionalities can not contribute to the mechanical properties of the material is that the urethane moieties are too small to crystallize and form hydrogen bonds.

Polyurethanes with a micro-phase separated morphology frequently exhibit good mechanical properties and are generally easy to process due to the relatively low melting point.

Mechanical properties of polyurethane ureas are usually even better resulting from the increased crystallizability and hydrogen bonding ability of the urea moieties. The polymers, however, frequently have melting points that are close to the degradation temperature, leading to a small processing window.

The polymers of the present invention, contain long urethane-based hard segments of uniform size. This results into a system wherein the hard segments have increased crystallizability and hydrogen bonding ability compared to "classical" polyurethanes. The mechanical properties are comparable to those of polyurethane ureas. However, the melting point is still rather low which makes processing relatively easy.

It should be noted that the uniformity of the urethane-based hard segments is the crucial factor for the mechanical properties of the materials. The preferred method for the synthesis of these polyurethanes should therefore be the reaction of the diol component with an excess of diisocyanate followed by reaction with the macro-diol (e.g. polycaprolactone or copolymers of L-lactide and caprolactone). In this process, trans-esterification of the soft segment with the chain extender is avoided, resulting into hard segments of uniform size.

As has been indicated above, the polyurethane of the invention comprises in the most general form diisocyante linked diol and polyester, more in particular linear random copolyester, components. The nature of the diol component is very important, especially with respect to the uniformity of the block-length. The diol and the (linear random co)polyester are connected to each other by diisocyanate, more in particular 1,4-butane diisocyanate.

The polyurethane of the present invention can be prepared by different processes. In a first process the diol component, i.e. the butanediol, hexaneddiol or diethylene glycol, or the reaction product of two molecules of the said

diol with 1,4-butanediisocyanate (BDO-BDI-BDO), is reacted with an isocyanate terminated polyester, i.e. the reaction product of the random polyester with an excess of BDI (BDI-polyester-BDI). By selection of the reaction conditions (temperature, time, catalyst, and the like) the molecular weight of the polyurethane may be selected.

In the alternative the diol component is end-capped with the BDI and reacted with the random copolyester.

According to a further method it is possible to end-cap the polyester with the isocyanate endcapped diol component resulting (in the case of a dihydroxy terminated polyester) in a prepolymer of the following composition:

OCN-E-NH-C(O)-D-C(O)-NH-E-NCO

This prepolymer can subsequently be reacted with water to yield a polyurethane urea according to the invention. This process provides the possibility to generate porous materials in situ, for example by mixing the prepolymer with salt and water, and letting the material react for some time at a suitable temperature. After leaching the salt from the material a porous polyurethane urea has been obtained, whereby part of the pores are provided by the salt and part by the $CO_2$ generated in the reaction of the prepolymer with the water.

The reactions between the various components are carried out under the conditions known to be suitable for the preparation of polyurethanes.

These processes all result in a useful biomedical polyurethane, having the advantageous properties cited above. It is to be noted that the use of an isocyanate endcapped diol has preference, especially in case the polyester component has the tendency to transesterify.

After the preparation of the base material it is possible to process it further, e.g. from a solution in an organic solvent such as dioxane, into shaped materials. For some applications it is useful to have a porous structure. This can be obtained by the method as described in De Groot

et al, Use of biodegradable polymer implants in meniscus reconstruction, Colloid Polym. Sci., 1990, **268**, 1073-1081. In case of the use of the polyurethane of the invention in meniscus reconstruction, it is useful to have porosities of 50 to 99 vol.%.

The diol component to be used in the present invention has to meet the requirement of uniform block-length. In practice this will mean that at least 90%, preferably at least 98% of the diol component molecules will have the same block-length. Suitable diol components can be based on 1,4-butanediol, 1,6-hexanediol or diethylene glycol. It is possible to use the diol as such, but it is also possible to use a reaction product of a diisocyanate (e.g. 1,4-butanediisocyanate) and two molecules of the diol (BDO-BDI-BDO). Optionally one may end-cap this reaction product with two molecules of BDI, resulting in a five-block, that can be used in the reaction with the linear random copolyester.

The polyester to be used in accordance with the invention will preferably be linear, more in particular be a random copolyester, and will have reactive endgroups. These endgroups may be hydroxyl or carboxyl. It is preferred to have a dihydroxy terminated copolyester, but hydroxy-carboxyl or dicarboxyl terminated copolyesters can also be used. The nature of the endgroups is determined by the type of comonomers, the amounts thereof, the type of starter (if used), and the reaction conditions. It is to be noted, that the molecular weight of the polyurethane in the present invention is not so crucial for obtaining the necessary mechanical properties, as is the case in the prior art. Accordingly, lower molecular weights often suffice.

Suitable monomers for the polyester are the cyclic monomers that can be polymerised under ring-opening polymerisation conditions. Examples are lactides, glycolides, trimethylene carbonate and/or ε-caprolacton. Preferred are lactide (D, L, D-L, meso) and ε-caprolacton. More in

particular a linear random copolyester having about equimolar amounts of ε-caprolacton and L-Lactide is preferred. Other possibilities include polyesters based on succinic acid and ethylene glycol or 1,4-butanediol, or on (co)polyesters of lactic acid. In case the polyester has to be linear, it can be prepared using a difunctional component (diol) as starter, but in case a three or higher functional polyol is used, star shaped polyesters may be obtained.

The conditions for preparing the polyesters are those known in the art.

The invention is now elucidated on the basis of the examples.

**Experimental**

*Materials*

L-lactide and ε-caprolactone were obtained from Hycail bv. (Noordhorn, The Netherlands) and used after standard purification. The catalyst stannous octoate ($SnOct_2$) was obtained from Sigma Corp. USA and used directly from the supplier. 1,4-Butane diisocyanate (DSM, Geleen, The Netherlands) was distilled under reduced nitrogen pressure; 1,4-butanediol (BDO, Acros Organics) from 4Å molecular sieves, dimethyl sulfoxide (DMSO, Acros Organics) from $CaH_2$.

*Prepolymer synthesis*

For the 50/50 L-lactide and ε-caprolactone, 20 gram of L-lactide (0.14 mol) was mixed with 16 gram ε-caprolactone (0.14 mol) under nitrogen atmosphere. 1.70 gram butanediol (18.87 mmol) and 40 mg stannous octoate were added as initiator and catalyst respectively. The mixture was polymerized for 24 hours at 130°C. $^1$H-NMR showed complete conversion.

*Block synthesis*

The isocyanate terminated urethane block (BDI/BDO/BDI) was prepared by reaction of butanediol with a six-fold excess of butanediisocyanate at 80°C without catalyst for 5 hours. The excess diisocyanate was removed by washing with dry hexane.

The hydroxyl terminated urethane block (BDO/BDI/BDO) was prepared by mixing butanediisocyanate with a six-fold excess of butanediol at 80°C without catalyst, for five hours. The excess butanediol was removed by washing with dry acetone.

*Polymerization*

The prepolymer (50/50 ε-caprolactone/L-lactide) or the diisocyanate end-capped prepolymer was dissolved in DMSO. The chain extender butanediol or block were dissolved in DMSO. The chain extender solution was added drop wise to the prepolymer solution under mechanical stirring. The total polymer concentration after chain extension was 5 w/w% in the case of butanediamine, 30 w/w% in the case of the isocyanate terminated block and 50 w/w% for butanediol and the hydroxyl terminated block.

*Characterization*

Intrinsic viscosities were measured using a Ubbelohde viscometer.

Calorimeter studies were carried out with a Perkin Elmer DSC 7 calorimeter. The scanning rate was 10°C per minute.

$^1$H-NMR (200 MHz) was used to characterize the blocks.

Tear strength and hysteresis were determined.

*Table 1*

| | Prepolymer | chain-extender |
|---|---|---|
| a | Isocyanate terminated prepolymer* | BDO |
| b | Prepolymer* | BDI/BDO/BDI |
| c | Isocyanate terminated prepolymer* | BDO/BDI/BDO |

*50/50 L-lactide/ε-caprolactone 2000

When the butanediisocyanate terminated prepolymer was chain extended with a BDI-BDO-BDI block (table 1, b), a polymer with an intrinsic viscosity of 1.0 dl/g could be made. The DSC thermogram of the polymer is shown in figure 1. The mechanical properties of the products based on a-c (table 1) are presented in table 2.

Table 2

| [η] (dl/g) | Modulus (MPa) | Tensile Strength (MPa) | Strain at break (%) | Tm (°C) | ΔH (J/g) | Tg ((°C) | Permanent Deformation (%) |
|---|---|---|---|---|---|---|---|
| 1.8 | 12 | 12 | 750 | 53 | 5.5 | -9 | 13.5 |
| 1.0 | 60 | 23 | 640 | 50, 92 | 8.6, 4.6 | -21 | 13.5 |
| 2.0 | 62 | 44 | 560 | 49,112 | 2.3, 16 | -5 | 10.0 |

These experiments show that the method b of table 1 provides products with better mechanical properties, than method a.

The role of the uniformity of the hard segments has also been demonstrated by the following example:

Polycaprolactone (M=2000) was end-capped with an excess of 1,4-butanediisocyanate. The excess of diisocyanate was removed by distillation. The resulting macro-diisocyanate was chain-extended with the BDO.BDI.BDO block. The resulting

polyurethane had an intrinsic viscosity of 2.00 dL/g and a modulus of 70 MPa.

When polycaprolactone (M=2000) was chain-extended with a BDI.BDO.BDI.BDO.BDI block, a polyurethane of identical composition was obtained. However, in this case trans-esterification reactions of the chain-extender with the polycaprolactone soft segement were avoided. This resulted into a polymer with an intrinsic viscosity of 1.00 dL/g and a modulus of 105 MPa. The lower viscosity of the polymer can be explained by the lower reactivity of the BDI.BDO.BDI.BDO.BDI block compared to the BDO.BDI.BDO block. However, the modulus has significantly increased. This is a result of the uniform hard segments. Hard segments of uniform size are more crystalline and thus more difficult to disrupt.

The absence of a melting endotherm at 60 °C provides additional evidence that by this method trans esterification reactions were avoided.

## Claims

1. Biomedical polyurethane based on diisocyanate linked polyester polymer and diol components, said diol component having a uniform block-length.

2. Biomedical polyurethane according to claim 1, having the following formula:

$$\text{-}(\text{A-B-C-B})\text{-}_n$$

wherein the B denotes diisocyanate moieties, A denotes a polyester moiety, C denotes a diol moiety and n is the number of recurring units.

3. Biomedical polyurethane according to claim 1 or 2 consisting of repeating units of the following formula

$$\{C(O)\text{-}NH\text{-}R_1\text{-}NH\text{-}C(O)\text{-}O\text{-}D\text{-}O\text{-}C(O)\text{-}NH\text{-}\ R_1\text{-}NH\text{-}C(O)\text{-}O\text{-}E\text{-}O\}_n,$$

wherein $R_1$ is an n-butylene moiety, D is a polyester moiety, E is an n-butylene diol, an n-hexylene diol or a diethylene glycol based moiety and n indicates the number of repeating units.

4. Polyurethane according to claim 1-3, wherein E is diol or an XYX reaction product of diol (X) and 1,4-butane-diisocyanate (Y).

5. Polyurethane according to claim 1-4, wherein the blocklength is the same for at least 90%, more in particular at least 98% of the diol units.

6. Polyurethane according to claim 1-5, wherein the polyester is based on a polyester prepared by ringopening polymerisation, preferably a random copolyester.

7. Polyurethane according to claim 6, wherein the random copolyester is a copolyester of lactide, glycolide, trimethylene carbonate and/or ε-caprolacton.

8. Polyurethane according to claim 1-6, wherein the polyester is based on lactic acid, succinic acid, diethylene glycol, 1,4-butanediol, 1,6-hexanediol and/or diethylene glycol.

9. Polyurethane according to claim 1-8, obtainable by a process comprising reacting the polyester and an isocyanate endcapped diol component, the ratio of polyester endgroups to isocyanate groups being at least two, followed by reacting the resulting prepolymer with water.

10. Polyurethane according to claim 7, based on a copolyester of lactide and ε-caprolacton containing 5 to 95, preferably 40-60 % of units of lactide and 5 to 95, preferably 40-60 % of units of ε-caprolacton, based on number.

11. 1,4-Butanediol, 1,6-hexane diol, or diethyleneglycol based diol component having a uniform blocklength, said component being an XYX reaction product of diol (X) and 1,4-butane-diisocyanate (Y).

12. Process for the preparation of a biomedical polyurethane according to claim 1-9 or 11, wherein the diol component is reacted with the reaction product of at least two moles of diisocyanate and the polyester.

13. Process for the preparation of a biomedical polyurethane according to claim 1-9 or 11, wherein the random copolymer is reacted with the reaction product of at least two moles of diisocyanate and the diol component.

14. Implants based on the biomedical polyurethanes according to claim 1-10, having a porosity of 50 to 99 vol.%.

15. Use of a polyurethane according to claim 1-10, as biodegradable polymer implant in meniscus reconstruction.

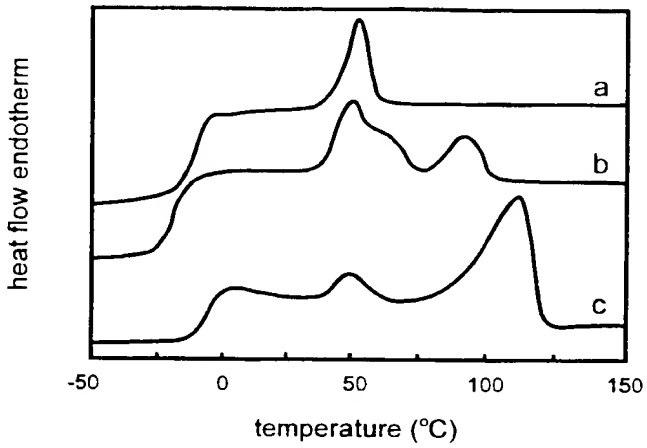


***Figure 1.*** *DSC thermogram of different ε-caprolactone and L-lactide based polyurethanes. a: Butanediisocyanate terminated copolymer prepolymer, chain extended with butanediol. b: Copolymer chain extended with butanediisocyanate end-capped butanediol block. c: 1,4-Butanediisocyanate terminated copolymer prepolymer, chain extended with butanediol end-capped 1,4-butanediisocyanate block.*

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/NL 99/00352

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C08G18/42 C08G18/80 A61L27/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C08G A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No |
|---|---|---|
| X | US 4 284 506 A (CASE BARTON C ET AL)<br>18 August 1981 (1981-08-18)<br>column 3, line 44 - column 8, line 21<br>examples 11,12,34-36; table 1<br>claims 1,4<br>--- | 1,2,5,6,<br>8,12 |
| X | GROOT DE J H ET AL: "USE OF POROUS POLYURETHANES FOR MENISCAL RECONSTRUCTION AND MENISCAL PROSTHESES"<br>BIOMATERIALS,<br>vol. 17, no. 2,<br>1 January 1996 (1996-01-01), pages 163-173, XP000551706<br>figures 5,12<br>---<br>-/-- | 1,2,6,<br>12,15 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 26 August 1999 | 06/09/1999 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office P B 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Neugebauer, U |

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | EP 0 295 055 A (YISSUM RES DEV CO)<br>14 December 1988 (1988-12-14)<br>page 2, line 4 - page 7, line 51<br>claims 1,18 | 1,2,6,8,<br>13 |
| P,X | WO 99 22780 A (FLODIN PER ;ARTIMPLANT DEV ARTDEV AB (SE); GISSELFAELT KATRIN (SE))<br>14 May 1999 (1999-05-14)<br>page 4, line 2 - page 5, line 38<br>example 1<br>claims 1,8,9 | 1,6 |
| A | GROOT DE J H ET AL: "NEW BIOMEDICAL POLYURETHANE UREAS WITH HIGH TEAR STRENGTHS"<br>POLYMER BULLETIN,<br>vol. 38, no. 2, February 1997 (1997-02),<br>pages 211-218, XP000678622 | 3,6,11 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/NL 99/00352

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 4284506 A | 18-08-1981 | AU 6430580 A | 02-07-1981 |
| | | BE 886862 A | 16-04-1981 |
| | | DE 3047832 A | 17-09-1981 |
| | | FR 2472392 A | 03-07-1981 |
| | | GB 2067580 A | 30-07-1981 |
| | | IT 1212428 B | 22-11-1989 |
| | | JP 56091757 A | 24-07-1981 |
| | | NL 8006885 A | 16-07-1981 |
| EP 0295055 A | 14-12-1988 | CA 1329854 A | 24-05-1994 |
| | | JP 1195862 A | 07-08-1989 |
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| | | AU 9564398 A | 24-05-1999 |
| | | SE 9704003 A | 04-05-1999 |

PATENT COOPERATION TREA

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | **FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
|---|---|---|
| P22294PC00 | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/NL 99/ 00352 | 04/06/1999 | 05/06/1998 |
| Applicant | | |
| RIJKSUNIVERSITEIT TE GRONINGEN.et,al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 03 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. ---

[ ] as suggested by the applicant.

[ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/NL 99/00352

A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C08G A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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|---|---|---|
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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 26 August 1999 | 06/09/1999 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Neugebauer, U |

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
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[redacted]mation on patent family members

[redacted]ernational Application No
PCT/NL 99/00352

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| | | JP 56091757 A | 24-07-1981 |
| | | NL 8006885 A | 16-07-1981 |
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| | | AU 9564398 A | 24-05-1999 |
| | | SE 9704003 A | 04-05-1999 |